PRODUCT MONOGRAPH

TIMPILO®

(timolol maleate and pilocarpine hydrochloride ophthalmic solution)

Sterile Ophthalmic Solution

ELEVATED INTRAOCULAR PRESSURE THERAPY

MERCK FROSST CANADA LTD.
KIRKLAND, QUEBEC, CANADA

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STERILE OPHTHALMIC SOLUTION

THERAPEUTIC CLASSIFICATION

ELEVATED INTRAOCULAR PRESSURE THERAPY

DESCRIPTION

TIMPILO® (timolol maleate and pilocarpine hydrochloride) is a fixed combination of timolol maleate 0.5% and pilocarpine hydrochloride 2% (TIMPILO® 2) or 4% (TIMPILO® 4). TIMPILO® is dispensed in a unique, two-chambered vial system. One chamber contains a concentrated solution of timolol and pilocarpine and the other chamber contains a diluent solution. The two solutions are mixed together prior to use. The resulting solution for administration has a pH of 6.4 to 6.8.

ACTIONS AND CLINICAL PHARMACOLOGY

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

Timolol maleate (S(-) enantiomer) is significantly metabolized after oral and

ophthalmic administration. The drug and the metabolites (hydroxyethylamino, hydroxyethylglycolamino derivatives and a third minor metabolite that results from the hydroxylation of a terminal methyl group on the tertiary butylamino moiety) are excreted primarily via the kidney. Based on correlation with debrisoquine metabolism, timolol metabolism is mediated primarily by cytochrome P-450 2D6. Timolol is moderately (<60%) bound to plasma proteins.

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice-daily topical administration of timolol maleate ophthalmic solution 0.5% for 8 days. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

By comparison to plasma concentrations (10 to 20 ng/mL) following oral 5 mg dose, it was estimated that timolol was approximately 50% bio-available systemically following intraocular administration.

Pilocarpine is a parasympathomimetic that directly stimulates cholinergic receptors. It produces contraction of the iris sphincter muscle, resulting in pupillary constriction (miosis); constriction of the ciliary muscle (resulting in increased accommodation) and a reduction in intraocular pressure associated with decreased resistance to aqueous humor outflow. Pilocarpine may also inhibit aqueous humor secretion.

Each of the two components decreases elevated intraocular pressure (IOP) by different but complementary mechanisms. Timolol lowers IOP primarily by reducing aqueous humor production. Pilocarpine lowers IOP primarily by enhancing the outflow of aqueous humor from the anterior chamber of the eye. Although pilocarpine, given alone requires administration four times a day, it has been shown that when formulated with timolol in TIMPILO® (timolol maleate and pilocarpine hydrochloride), administration twice daily is adequate.

INDICATIONS AND CLINICAL USE

TIMPILO® (timolol maleate and pilocarpine hydrochloride) is indicated for the reduction of elevated intraocular pressure in patients whose IOP is not adequately controlled on monotherapy with a beta-adrenergic receptor blocking agent or pilocarpine or when concomitant therapy is appropriate.

In clinical trials, it has been shown to reduce intraocular pressure in:

- patients with ocular hypertension when miosis is not a contraindication
- patients with chronic open-angle glaucoma

CONTRAINDICATIONS

Bronchospasm, including bronchial asthma, or a history of these conditions, or chronic obstructive pulmonary disease.

Sinus bradycardia, second and third degree atrioventricular block, overt congestive cardiac failure, cardiogenic shock.

Conditions in which miosis is undesirable: malignant glaucoma, peripheral anterior synechia, trauma, acute-inflammatory disease of anterior chamber, glaucoma occurring or persisting after extracapsular cataract extraction when posterior synechia may occur, etc.

Hypersensitivity to any component of this product.

WARNINGS

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

TIMPILO® (timolol maleate and pilocarpine hydrochloride) should be used with caution in patients with diabetes, especially labile diabetes (see PRECAUTIONS).

Following administration of timolol ophthalmic solution, severe respiratory reactions and cardiac reactions have been reported, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure.

PRECAUTIONS

Cardio vascular Function

Cardiac failure should be controlled before beginning therapy with TIMPILO® (timolol maleate and pilocarpine hydrochloride). In patients with a history of cardiac disease signs of cardiac failure should be watched for and pulse rate should be checked.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMPILO®, alternative therapy should be considered.

Eye Accommodation

Miosis usually causes difficulty in dark adaptation. Caution should be exercised in night driving and other hazardous activities in poor illumination.

Choroidal Detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide or combination) after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

Contact Lenses

TIMPILO® contains the preservative benzalkonium chloride which may be absorbed by soft contact lenses. Therefore, TIMPILO® should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than15 minutes after use.

Risk from Anaphylactic Reaction

While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic, or therapeutic. These patients may be more resistant to treatment of anaphylactic reactions with the usual doses of epinephrine since timolol may blunt the beta-agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

Muscle Weakness

Beta-adrenergic blockage has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Use in Pregnancy

TIMPILO® has not been studied in human pregnancy. The use of TIMPILO® in pregnancy requires that the anticipated benefit be weighed against potential hazards.

The use of systemic beta-blockers is not recommended during pregnancy.

Nursing Mothers

Timolol is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

Safety and effectiveness in children have not been established.

Drug Interactions

The use of two topical beta-adrenergic blocking agents is not recommended.

Beta-Adrenergic Blockers

Patients already receiving a beta blocker systemically and who are given TIMPILO® should be observed for a potential additive effect on the intraocular pressure or on the known systemic effects of beta blockers (hypotension and/or bradycardia). The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Channel Blockers or Catecholamine-depleting Drugs

Calcium blockers or catecholamine-depleting drugs such as reserpine, may produce additive effects, hypotension and/or marked bradycardia, with possible vertigo, syncope or postural hypotension. Intravenous calcium blockers should be used with caution in patients receiving beta blockers.

Quinidine

Potentiated systemic beta blockage (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine

Oral β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the β-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by β-blocker therapy, the introduction of β-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

Information to Be Provided to the Patient

- Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice about continuing treatment with TIMPILO®.
- Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

- Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

- There have been reports of bacterial keratitis associated with the use of multiple

dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithalial surface.

- Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second-or third-degree atrioventricular block, or cardiac failure should be advised not to take this product (see CONTRAINDICATIONS).

- Patients Wearing Contact Lenses:
  TIMPILO® contains benzalkonium chloride as a preservative. This preservative may be absorbed by soft contact lenses. If you wear soft contact lenses consult your doctor before using TIMPILO®.
  Patients should be instructed to remove their lenses before application of the drops and not to re-insert the lenses earlier than 15 minutes after use.

ADVERSE REACTIONS

TIMPILO® (timolol maleate and pilocarpine hydrochloride) is generally well-tolerated. In clinical studies of TIMPILO® the adverse experiences reported were mainly well-known pilocarpine side effects: blurring of vision, difficulty with dark adaptation, headache/brow-ache and ocular irritation (see below).

Potential Side Effects

Side effects reported in clinical and post-marketing experience with TIMOPTIC® (timolol maleate ophthalmic solution, Merck Frosst Std.), systemic BLOCADREN® (timolol maleate tablets, Merck Frosst Std.), other timolol maleate formulations and pilocarpine ophthalmic solution may be considered potential side effects of TIMPILO® Ophthalmic Solution.

The following adverse reactions have been reported with ocular administration of this or other timolol maleate formulation, either in clinical trials or since the drug has been marketed.

Special Senses

Signs and symptoms of ocular irritation: including burning and stinging, conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity and dry eyes.

Visual disturbances: including diplopia, ptosis, choroidal detachment following filtration surgery (see PRECAUTIONS).

Tinnitus.

Cardiovascular

Aggravation or precipitation of certain cardiovascular pulmonary and other disorders presumably related to effects of systemic beta blockade has been reported (see CONTRAINDICATIONS and PRECAUTIONS). These include bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, palpitation, cardiac arrest ,edema, claudication, Raynaud's phenomenon, cold hands and feet. Congestive heart failure, and in insulin-dependent diabetics masked symptoms of hypoglycemia have been reported rarely.

Respiratory

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough.

Miscellaneous

Headache, asthenia, fatigue, chest pain.

Integumentary

Alopecia, psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity

Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localized and generalized rash.

Nervous System/Psychiatric

Dizziness, depression, increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, memory loss, paresthesia.

Digestive

Nausea, diarrhea, dyspepsia, dry mouth.

Urogenital

Decreased libido, Peyronie's disease.

Immunologic

Systemic lupus erythematous.

Timolol-Systemic

Side effects reported in clinical experience with systemic timolol maleate may be considered potential side effects of ophthalmic solution TIMPILO®.

Clinical Laboratory Tests

Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in blood urea nitrogen, serum potassium and serum uric acid and triglycerides, and slight decreases in hemoglobin and hematocrit and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

Pilocarpine Hydrochloride Ophthalmic Solution

Ocular

Ciliary spasm, conjunctival vascular congestion, lacrimation, temporal or supra-orbital headache, induced myopia, reduced visual acuity in poor illumination (especially in the elderly and in patients with lens opacities), retinal detachment (especially in young myopic patients). Lens opacity may occur with prolonged use of pilocarpine.

Systemic

Extremely rare, but have included hypertension, tachycardia, bronchospasm, pulmonary edema, salivation, sweating, nausea, vomiting and diarrhea.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been reports of inadvertent overdosage with TIMOPTIC® (timolol maleate ophthalmic solution, Merck Frosst Std.) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

The following therapeutic measures should be considered:

1) Gastric lavage: If ingested.

2) Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

3) Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.

4) Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

5) Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.

6) Heart block (second-or third-degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

Pilocarpine

Cholinergic systemic effects are extremely rare with ocular use of pilocarpine (see ADVERSE REACTIONS). If accidentally swallowed, pilocarpine is readily absorbed from the alimentary tract, and if a large amount is ingested cholinergic symptoms may appear, including salivation, lacrimation, nausea, vomiting, headache, mental confusion, visual disturbances, abdominal colic, diarrhea, bronchospasm, and hypotension. Dehydration and shock may develop. Respiratory depression has been reported in severe cases of pilocarpine poisoning.

Treatment is with general measures and atropine.

DOSAGE AND ADMINISTRATION

Recommended dosing for TIMPILO® (timolol maleate and pilocarpine hydrochloride) is as follows:

Instill one drop of TIMPILO® 2 (timolol maleate 0.5% and pilocarpine hydrochloride 2%) twice daily in the affected eye. If the clinical response is inadequate the dosage

may be increased by using one drop of TIMPILO® 4 (timolol maleate 0.5% and pilocarpine hydrochloride 4%) twice daily.

When a patient is transferred from prior therapy, the previously-administered agents should be discontinued after proper dosing on one day, and treatment with TIMPILO® started on the following day.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

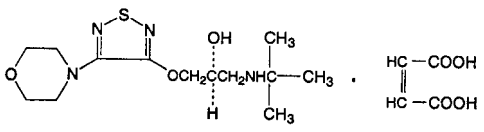
Tradename: TIMPILO®

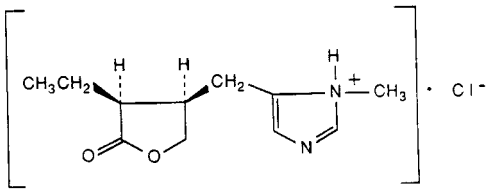
Common names: Timolol maleate and pilocarpine hydrochloride

Chemical names:

Timolol maleate	**Pilocarpine Hydrochloride**
(*S*)-1[(1,1-dimethylethyl) amino]-3-[[4-(4-morpholinyl) -1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) (salt)	(3*S*-cis)-3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl) methyl]-2(3H)-furanone monohydrochloride.

Structural formulae:





Molecular formulae:

$C_{13}H_{24}N_4O_3S.C_4H_4O_4$	$C_{11}H_{16}N_2O_2.HCl$

Molecular weights:

432.49	244.72

Descriptions:

Timolol maleate is a beta-adrenergic receptor blocking agent. It possesses an asymetric carbon atom in its structure and is provided as the levo isomer. It is a white odourless, crystalline powder which is soluble in water, methanol and alcohol.

Pilocarpine hydrochloride is a cholinergic agent. It is a white odourless crystalline powder or may occur as colourless crystals.

II. COMPOSITION

Each mL of constituted TIMPILO® 0.5 - 2.0% contains 6.8 mg of timolol maleate (5.0 mg of timolol) and 20.0 mg of pilocarpine hydrochloride. Each mL of TIMPILO® 0.5 - 4.0% contains 6.8 mg of timolol maleate (5.0 mg of timolol) and 40.0 mg of pilocarpine hydrochloride. Non-medicinal ingredients: sodium phosphate dibasic dodecahydrate, sodium phosphate monobasic dihydrate, and water for injection. Benzalkonium chloride 0.01% is added as preservative.

III. STABILITY AND STORAGE RECOMMENDATIONS

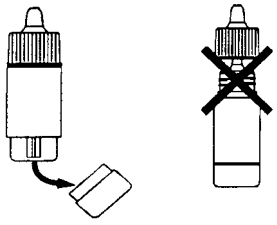
Prior to mixing solutions, avoid temperatures above 30°C. After mixing, TIMPILO® 2 and TIMPILO® 4 are stable for 28 days when stored at room temperature (15°C - 25°C). Protect from light and freezing.

IV. INSTRUCTIONS FOR USE

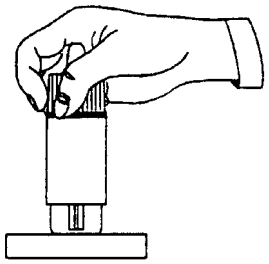
Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.

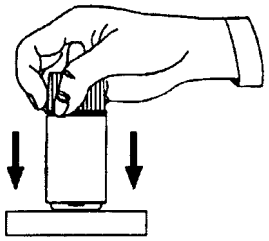
There are two solutions in the vial that are separated by a plug. Before using TIMPILO® for the first time, these solutions must be mixed together following these five steps:

1. Remove the clear plastic protective sleeve from the entire vial by pulling the tab near the top of the cap. Remove the white bottom cap to expose the bottom chamber containing the solution. DO NOT unscrew the top cap at this time.

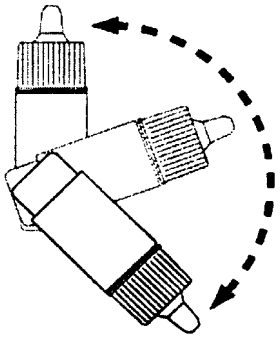


2. Against a hard surface (e.g., a table), push the vial down toward the surface. A slight “popping” sound can usually be heard as the plug, separating the two solutions, is displaced. The contents are now ready for mixing.

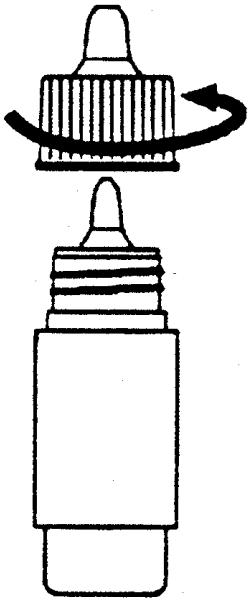




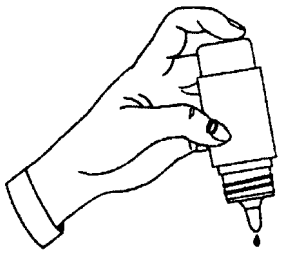
3. Invert the container several times to mix the contents.



4. Unscrew the top cap.



5. Hold the container in an inverted position and gently depress the bottom of the vial to expel and discard two drops. The solution is now ready for use.



6. Instill as directed by physician in affected eye(s).

7. Replace the bottom and top caps after use.

There is no need to repeat steps 1 through 5 each time TIMPILO® is used: The contents of the bottle do not have to be mixed again.

AVAILABILITY OF DOSAGE FORMS

TIMPILO® (timolol maleate and pilocarpine hydrochloride) is dispensed in a unique, two-chambered vial system. One of the chambers contains a concentrated solution of timolol and pilocarpine at a pH of approximately 3.7. This low pH prevents the hydrolysis of pilocarpine prior to dispensing. The other chamber contains a diluent solution with a pH of approximatively 8.0 for TIMPILO® 2 and approximatively 9.0 for TIMPILO® 4. The two solutions are separated by an internal plug.

Prior to use, the two solutions are mixed together. The resulting solution for administration has a pH of 6.4 to 6.8.

1. TIMPILO® 2, contains 6.8 mg of timolol maleate, equivalent to 5.0 mg (0.5%) of timolol and 20.0 mg (2.0%) of pilocarpine hydrochloride per mL of the final solution is supplied as follows:

   White, opaque, polyethylene ophthalmic dispenser containing 5 mL after

reconstitution.

2. TIMPILO® 4, contains 6.8 mg of timolol maleate, equivalent to 5.0 mg (0.5%) of timolol and 40.0 mg (4.0%) of pilocarpine hydrochloride per mL of the final solution is supplied as follows:

   White, opaque, polyethylene ophthalmic dispenser containing 5 mL after reconstitution.

PHARMACOLOGY

Timolol Maleate

Timolol maleate reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided. When changing patients from miotics to timolol maleate a refraction might be necessary when these effects of the miotic have passed.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially

dangerous.

Pilocarpine

Pilocarpine hydrochloride is a cholinergic substance which causes a significant reduction of intraocular pressure. This is thought to be due to contraction of the ciliary muscle, which in turn transmits increased tension to the scleral spur, resulting in a decrease in the resistance of aqueous outflow as the trabecular outflow channels become enlarged.

TOXICOLOGY

Acute Toxicity (LD_{50})

Male and female mice were used to evaluate the acute oral toxicity of timolol maleate and pilocarpine hydrochloride.

Drug	Sex	Route of Administration	LD_{50} mg/kg
Timolol maleate	F	Oral	1,115
Timolol maleate	M	Oral	1,171
Pilocarpine HCl	F	Oral	281
Pilocarpine HCl	M	Oral	265

Signs of toxicity observed with timolol tested alone consisted of tremors, decreased activity and bradypnea. Signs of toxicity observed with pilocarpine tested alone consisted of ataxia, salivation, diarrhea, and tremors.

Ocular Effects

Ophthalmologic changes consisting of slight transient ocular reactions such as miosis, slight blinking and slight redness of bulbar conjunctiva, were observed in rabbits administered TIMPILO® (timolol maleate and pilocarpine hydrochloride) topically for 4 weeks.

Chronic Toxicity

Information regarding chronic toxicity for timolol maleate and pilocarpine hydrochloride ophthalmic solutions is available in their respective Product Monograph.

REFERENCES

1. Airaksinen PJ. The long-term hypotensive effect of timolol maleate compared with the effect of pilocarpine in simple and capsular glaucoma. Acta Ophthalmol 1979;57:425-34.

2. Calissendorff M. Timolol-maintenance treatment. Acta Ophthalmol 1980;58:933-46.

3. Katz IM, Hubbard WA, Getson AJ, Gould LA. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. Invest Ophthalmol 1976;15(6):489-92.

4. Kerty E, Horven I. Glaucoma treatment with timolol. Acta Ophthalmol 1978;56:705-14.

5. Mackie JA, Seal DV, Pescod JM. Beta-adrenergic receptor blocking drugs: tear lysozyme and immunological screening for adverse reaction. Br J Ophthalmol 1977;61:354-9.

6. Maclure GM, Vogel R. The effect on diurnal control of IOP of co-administration of pilocarpine and TIMOPTOL. New Trends in Ophthalmology 1987;11:79-86.

7. Ober M, Scharrer A. The effects of timolol and parasympathicomimetica in the treatment of elevated intraocular pressure. Graefes Arch Clin Exp Ophthalmol 1979;211:59.

8. Strempel I. Timolol: Long-term results, tolerance test and early morning measurements. Klin Hbl Augenheilk 1979;175:619-26.

9. Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. Can Med Assoc J 1987;136(9):929-33.

10. Yablonski ME, Zimmerman TJ, Waltman SR, Becker B. A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. Exp Eye Res 1978;27:135-42.

11. Zimmerman TJ. Timolol maleate - a new glaucoma medication? Invest Ophthalmol Vis Sci 1977;16(8):687-8.

12. Zimmerman TJ, Harbin, R, Pett M, Kaufman HE. Timolol and facility of outflow Invest Ophthalmol Vis Sci 1977;16(7):623-4.

13. Zimmerman TJ, Kaufman HE. Timolol a β-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol 1977;95:601-4.

14. Zimmerman TJ, Kaufman HE. Timolol: Dose response and duration of action Arch Ophthalmol 1977;95:605-7.

15. Zimmerman TJ, Kaufman HE. Timolol: A new drug for the treatment of Glaucoma? Symposium on Ocular Therapy 1977;10:69-76.

16. Vela MA, Campbell DG. Hypotony and ciliochoroidal detachment following pharmacologic aqueous suppressant therapy in previously filtered patients.

Ophthalmology 1985;92(1):50-7.

17. Berke SJ, Bellows AR, Shingleton BJ, Richter CU, Hutchinson BT. Chronic and recurrent choroidal detachment after glaucoma filtering surgery. Ophthalmology 1987;94(2):154-62.

18. Dinai Y, Sharir M, Navey (Floman) N, Halkin H. Bradycardia induced by interaction between quinidine and ophthalmic timolol. Ann Intern Med 1985;103(6):890-1.

19. Edeki TI, He H, Wood AJJ. Pharmacogenetic explanation for excessive β-blockade following timolol eye drops. JAMA 1995;274(20):1611-3.

20. Higginbotham EJ. Topical β-adrenergic antagonists and quinidine: A risky interaction. Arch Ophthalmol 1996;114(6):745-6.

21. Kaila R, Huupponen R, Karhuvaara S, Havula P, Scheinin M, Iisalo E, Salminen L. β-blocking effects of timolol at low plasma concentrations. Clin Pharmacol 1991;49(1):53-8.